FORM PTO-1390 (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

ATTORNEY'S DOCKET NUMBER: GEI-067

U.S. APPLICATION NO (If known, see 37 CFR 1.5):

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

INTERNATIONAL APPLICATION NO	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR97/01792	October 8, 1997	October 8, 1996

TITLE OF INVENTION: HORMONAL COMPOSITION CONSISTING OF AN ESTROGEN COMPOUND AND OF A PROGESTATIONAL COMPOUND

APPLICANT(S) FOR DO/EO/US: LANQUETIN et al

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. [ ] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. [ ] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [X] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [ ] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [ ] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)). UNEXECUTED
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. [X] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND or SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: Amended Claims (2 pages)with English Translation

U.S. APPLICATION (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/284147	PCT/FR97/01792	GET-067

17. [X] The following fees are submitted:

	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO $830.00	$ 970.00	
International preliminary examination fee paid to USPTO (37 CFR 1.482) $640.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) $710.00		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37CFR 1.445(a)(2)) paid to USPTO..... $950.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4)..... $90.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 970.00	
Surcharge of $130.00 for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	Number Filed	Number Extra	Rate	
Total Claims	-20 -		X $22.00	$
Independent Claims	-3 -		X $74.00	$
Multiple dependent claims(s) (if applicable)			+ $230.00	$
TOTAL OF ABOVE CALCULATIONS =				$ 970.00
Reduction by 1/2 for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$
SUBTOTAL =				$ 970.00
Processing fee of $130.00 for furnishing the English translation later the [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f)). +				$
TOTAL NATIONAL FEE =				$ 970.00
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				$ 40.00
TOTAL FEES ENCLOSED =				$ 1010.00
			Amount to be: refunded	$
			charged	$

a. [XX] A check in the amount of $1010.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $_____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 02-2275. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:
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New York, Ny 10016

SIGNATURE

Charles A. Muserlian
NAME

19,683
REGISTRATION NUMBER

Form PTO-1390 (REV. 5-93)

Our Ref.: GEI-067

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
LANQUETIN et al
PCT/FR97/01792
Serial No.:
Filed: Concurrently Herewith
For: HORMONAL...COMPOUND

PCT Date: October 8, 1997

600 Third Avenue
New York, NY 10016

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Please amend this application as follows:

IN THE AMENDED CLAIMS:

Amended claim 3, line 1, cancel "or claim 2".

Amended claim 4, line 1, cancel "one of claims 1 to 3" and insert --claim 1--.

Amended claim 9, line 1, cancel "claims 1 and 8" and insert --claim 1--.

Cancel claims 11 to 15 and add the following claims.

--16. A method of treating estrogenic deficiencies in post-menopausal women comprising orally administering to post-menopausal women estrogenically stimulating amount of a composition of claim 1.--

--17. A method of treating osteoporosis and cardiovascular illnesses in post-menopausal women comprising orally administering to post-menopausal women a composition of claim 1 in an amount sufficient to treat said conditions.--

--18. A method of stopping ovulation in women comprising orally administering to women during their ovulation period an amount of a composition of claim 1 to stop ovulation.--

--19. The method of claim 16 wherein the composition is administered continuously.--

--20. The method of claim 16 wherein the composition is administered intermittently.

REMARKS

The amendment is submitted to remove multiple dependency from the claims and to present method of use claims that conform to the

American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

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CAM:sd
Enclosure: Return Receipt Postcard

HORMONAL COMPOSITION CONSISTING OF AN OESTROGEN COMPOUND AND OF A PROGESTATIONAL COMPOUND

LABORATOIRE THERAMEX

ABSTRACT OF THE TECHNICAL CONTENT OF THE INVENTION

The present invention relates to the field of therapeutic chemistry and more particularly to the field of hormonal pharmaceutical techniques.

A more precise subject of the invention is new hormonal pharmaceutical compositions characterized in that they are formed by an estroprogestative combination constituted by an estrogen compound and a progestative compound, in combination or in a mixture with one or more pharmaceutically acceptable, inert, non toxic excipients, intended for administration by oral route.

The present invention also relates to the use of an estroprogestative mixture in which the estrogenic component and the progestative component are administered in a combined fashion. The combined combination can be prescribed in a continuous or intermittent fashion, with a view to the realisation of a composition intended for the treatment of estrogenic deficiencies, for the prevention of osteoporosis and carciovascular illnesses in post-menopausal women or also for stopping ovulation in women during their period of ovarian activity.

A subject of the invention is also a preparation process for these new estroprogestative pharmaceutical compositions.

HORMONAL COMPOSITION CONSISTING OF AN OESTROGEN COMPOUND AND OF A PROGESTATIONAL COMPOUND

The present invention relates to the field of therapeutic chemistry and more particularly to the field of hormonal pharmaceutical techniques.

A more precise subject of the invention is new pharmaceutical compositions formed by an estroprogestative combination with a view to the correction of estrogenic deficiencies in natural or artificial menopauses or in order to stop ovulation in women during their period of ovarian activity.

In particular a subject of the invention is an estroprogestative combination, characterized in that it is constituted by unit doses containing the combination of a progestative and an estrogen, the two components being present simultaneously in each medicinal dose.

This combination is intended to be administered by oral route.

As is known, the life expectancy of women has passed in less than a century from 50 to 80 years, whilst the average age for the onset of the menopause has remained unchanged. Therefore, women spend a third of their life in a state of estrogenic deficiency which is the origin of the increase in risk of osteoporosis and cardiovascular illnesses.

Sequential replacement treatment for the menopause cures the climateric symptomology and prevents osteoporosis and the onset of illnesses. It creates artificial cycles which are followed by a withdrawal bleeding. This therapeutic schema quite particularly suits women for whom the menopause is recent but it is not always well accepted in the long term, which in part explains the poorer observance of treatment (DRAPIER FAURE E.; Gynécologie. 1992, 43: 271-280).

In order to overcome this drawback, combined combinations have been perfected where the two components are taken simultaneously, the progestative having the effect of permanently opposing the proliferative action of the estrogen on the endometrium,

by creating an atrophy of the endometrium and as a consequence, the absence of withdrawal bleeding (HARGROVE J.T., MAXSON W.S., WENTZ A.C., BURNETT L.S., Obstet Gynecol, 1989, 73: 606-612).

This "no periods" schema more particularly suits women for whom the menopause is already well in the past. It can be prescribed in courses of sequential combinations in order to improve the long-term observance of replacement hormone treatment for the menopause.

The dose of progestative to be used in a combined replacement treatment is in general deduced from that which is usually prescribed in sequential schemata. In the latter the dose chosen is that which gives over the long term less than 1% endometrial hyperplasia when the progestative is administered discontinuously, more than 10 days per cycle, in post-menopasual women under replacement estrogenotherapy (WHITEHEAD et al., J. reprod. Med, 1982, 27: 539-548, PATERSON et al, Br Med J, 1980, 22 March: 822-824).

In the combined treatment, these same progestatives were used at half the dose judged to be effective during a sequential treatment: this is the example of the micronized progesterone, didrogesterone (FOX H., BAAK J., VAN DE WEIJER P., AL-AZZAWI E., PATERSON M., JOHNSON A., MICHELL G., BARLOW D., FRANCIS R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr 119) and medroxyprogesterone acetate (BOCANERA R., BEN J., COFONE M., GUINLE I., MAILAND D., SOSA M., POUDES G., ROBERTI A., BISO T., EZPELETA D., PUCHE R., TOZZINI R., 7th International Congress on the Menopause, Stockholm, 20-24 June 1993, abstr 40) which were used at doses of 100, 10 and 5 mg/day respectively, with encouraging results on the clinical and endometrial level.

Among the progestatives, nomegestrol acetate appeared to be one of the most effective. Nomegestrol acetate is a non-androgenic progestative derived from 19-nor progesterone, its use in sequential administration during the menopause at the dose of 5 mg/day, 12 days per cycle, in combination with different types of estrogens, allows endometrial hyperplasia to be prevented as shown by a multicentre study on 150

women for one year (THOMAS J.L., BERNARD A.M., DENIS C., 7th International Congress on the Menopause, Stckholm, 20-24 June 1993, abstr 372).

The absence of hyperplasia was confirmed in a study where the nomegestrol acetate was administered at the same dose, 14 days per cycle, in women treated with percutaneous estradiol (BERNARD A.M. et al. Comparative evaluation of two percutaneous estradiol gels in combination with nomegestrol acetate in hormone replacement therapy. XIV World Congress of Gynecology and Obstetrics, FIGO, Montreal, 24-30 September 1994).

The combined treatment is more often used in a continuous fashion, i.e. without interruption. However some people are in favour of using it in an intermittent fashion, for example 25 days per month (BIRKAUSER M. ET AL; Substitution hormonale: une indication bien posée et des schémas de traitement individuels sont déterminants pour le succès du traitement, Méd. et Hyg., 1995, 53: 1770-1773). The aim of the therapeutic interruption is to remove the inhibition exercised by the progestative on the synthesis of the estradiol and progesterone receptors and in this way to avoid the lowering of receptivity of the hormono-dependant tissues.

The progesterone used according to the present invention is nomegestrol acetate which is active by oral route.

The estrogen used is free or esterified estradiol, or equine conjugated estrogens which are presented according to a formulation which is active by oral route and in particular estradiol valerate.

Nomegestrol acetate and free or esterified estradiol or equine conjugated estrogens are administered in one of the forms which permit administration by oral route: gelatine capsules, capsules, pills, sachets of powder, tablets, coated tablets, sugar-coated tablets etc..

The present invention is characterized in that it is constituted by a new estroprogestative combination, which is active by oral route and administered in a combined manner. A subject of the present invention is also its use in the correction of estrogenic deficiencies, in the prevention of osteoporosis and cardiovascular illnesses in

post-menopausal women, or in stopping ovulation in women during their period of ovarian activity.

The compositions according to the invention based on nomegestrol and free or esterified estradiol or equine conjugated estrogens are administered in a continuous or intermittent fashion, from 21 to 25 days per month.

According to a particular implementation of the invention the compositions contain a quantity of nomegestrol acetate ranging form 1.5 to 3.75 mg and a quantity of free or esterified estradiol or equine conjugated estrogens ranging from 0.5 to 3 mg. Preferably, the optimal formulations contain 2.5 mg of nomegestrol acetate combined with : either 1.5 mg of free estradiol or 2 mg of estradiol ester or 0.625 mg of equine conjugated estrogens, per daily dose.

This combined administration method can have several therapeutic indications. In post-menopausal women, the estroprogestative combination is intended to compensate for the functional disorders brought about by hypoestrogenism of the menopause, while maintaining an atrophy of the endometrium and avoiding in a majority of them the appearance of withdrawal bleeding.

In women during the period of ovarian activity, young or in the years preceding the menopause, the cyclic administration of the hormonal combination is capable of stopping ovulation and of exercising a contraceptive effect insofar as it has been proved that nomegestrol is capable of stopping the ovulation peak of LH and FSH, starting from 1.25 mg/day (BAZIN B. et al, Effect of nomegestrol acetate, a new 19-norprogesterone derivative on pituitary ovarian function in women. Br. J. Obstet. Gynaecol., 1987, 94: 1199-1204). When the hormonal combination is given for a contraceptive purpose, the aim of nomegestrol acetate is to stop ovulation and for the estrogenic compound to compensate for hypoestrogenia and ensure a better control of the cycle.

A subject of the present invention is also a process for obtaining new pharmaceutical compositions.

The obtaining process according to the invention consists of mixing the active ingredients: nomegestrol acetate and free or esterified estradiol or equine conjugated estrogens with one or more pharmaceutically acceptable, non-toxic , inert excipients.

Among the excipients which can be mentioned are binding and solubilizing agents, compression agents, disintegration agents and slip agents.

This mixture can be subjected to direct compression or to several stages of compression in order to form tablets which, if desired, can have their surface protected by a film, by lacquering or coating. The production of tablets by direct compression allows a maximum reduction in the proportion of diluting agents, binding agents, disintegration agents and slip agents.

The production of gelatine capsules can be carried out by mixing the active ingredients with an inert diluant and a slip agent.

The tablets contain, in particular, mass diluting agents such as lactose, sorbitol for direct compression, marketed under the name NEOSORB 60, Palatinite which is a registered trademark for designating an equimolar mixture of the isomer of -D-glucopyranosido 1,6-mannitol and -D-glucopyranosido 1,6-glucitol crystallized with two molecules of water, mannitol, sorbitol or the mixture lactose/PVP sold under the name Ludipress.

The compression binding agents are in general microcrystalline celluloses such as those sold under the name AVICEL PH 101 or AVICEL PH 102.

The polyvinylpyrrolidone plays an important role and facilitates the agglomeration of the powders and the compressibility of the mass. To this end polyvinylpyrrolidones are used with a molecular weight comprised between 10000 and 30000 such as Povidone, Kollidon of a grade comprised between 12 and 30.

The mixture also contains slip or anti-electrostatic agents so that the powder does not agglomerate in the feed hoppers. In this respect, colloidal silicas can be mentioned which are sold under the name AEROSIL 100 or AEROSIL 200.

The mixture also contains disintegration agents which allow disintegration or crumbling which conforms to pharmaceutical standards. There can be mentioned as useful disintegration agents, polymers of cross-linked vinylpyrrolidones such as those sold under the names Polyplasdone or Polyclar AT, carboxymethylamidons such as

those sold under the names Amigel or Explotab, cross-linked carboxymethylcelluloses or croscarmelloses such as the compound sold under the name AC-DI-SOL>

In addition, the preparation contains lubrication agents which facilitate the compression and ejection of the tablet from the tablet compressing machine. There can be mentioned as lubrication agents, glycerol palmitostearate sold under the name Precirol, magnesium stearate, stearic acid or talc.

After compression the tablets can be coated in order to ensure their storage or to facilitate their deglutination.

The coating agents are either of cellulose origin such as cellulose phthalate (Sepifilm, Pharmacoat), or of polyvinyl origin of Sepifilm ECL type, or of saccharose origin such as the sugar for sugar-coating of Sepisperse DR, AS, AP OR K (coloured) type.

The tablets, whether coated or not, can, in addition, be surface or bulk coloured, by plant or synthetic colouring agents (for example chinolin yellow lacquer or E 104).

The proportions of the different constituents varies according to the type of tablet to be produced.

The content of active ingredients can vary from 1.5 to 3.75 mg for nomegestrol acetate and from 0.5 to 3 mg for free or esterified estradiol or for equine conjugated estrogens.

The dilution agents vary from 20 to 75% of the total mass, the slip agents from 0.1 to 2% of the total mass, the compression binding agents vary from 2 to 20%, the polyvinylpyrrolidone from 0.5 to 15%, the disintegration agents vary from 2 to 5.5% for the cross-linked polyvinylpyrrolidone or the carboxymethylamidon, from 2.0 to 3.0% for the croscarmellose.

The quantities of lubricating agents vary as function of the type of agents from 0.1 to 3.0%.

The compositions according to the invention are intended to be administered once per day. However, depending on the therapeutic requirements, administration can be split up (twice per day) or on the other hand, repeated (two tablets per day).

The following examples illustrate the invention. They in no way limit it.

EXAMPLE I

Tablets with 4 mg of active ingredient

Active ingredients:	- estradiol	1.5 mg
	- nomegestrol acetate	2.5 mg
Microcrystalline cellulose		22.4 mg
(marketed under the name AVICEL PH 102)		
Lactose		60 mg
Polyvinylpyrrolidone		8.4 mg
Colloidal silica		1.2 mg
Glycerol palmitostearate		3.6 mg
Colouring agent E.104		0.4 mg

for a tablet completed at an average weight of 100 mg.

EXAMPLE II

Study of the clinical tolerance during two continuous combined schemata of hormone replacement therapy for the menopause

The pilot study is carried out over 24 weeks on two parallel groups subjected to treatments A and C:

Treatment A

- Nomegestrol acetate 2.5 mg/day every day + percutaneous 17β-estradiol 1.5 mg/day every day.
- The nomegestrol acetate is administered in the form of tablets and the percutaneous 17β-estradiol in the form of a gel.

Treatment C

- Nomegestrol acetate 2.5 mg/day every day + estradiol valerate 2 mg/day every day.
- The estradiol valerate is administered in the form of tablets.

The pilot study is intended to evaluate the endometrial clinical tolerance during the use of the two hormone replacement therapy schemata for the menopause so-called "without periods" combining in a continuous combined fashion treatment A or C. The endometrial clinical tolerance is evaluated from the presence or not of occurences of vagina bleeding, their intensity, their frequency, from data acquired from endovaginal echographical examination etc..

Also, another aim of this study is to assess the general clinical tolerance (weight, blood pressure, mammary symptoms), biological tolerance (Formule Numeration Sanguine (blood count), glycemia, cholesterol...), as well as the observance of treatment.

The selection of subjects is carried out as a function of "inclusion" criteria. These criteria are to do:

- with the menopause:

women over 50 years old are included who have had a natural menopause expressed clinically by an amenorrhea greater than 12 months and less than 10 years, the women having had a natural menopause confirmed biologically by quantitative analysis of FSH (Follicle stimulating hormone) and estradiol (i.e. plasmatic FSH $\geq$ 20 IU/I, plasmatic E_2 $\leq$ 0.11 nmol/l).

- with women:

women who have not had hysterectomies are included, whose Quetelet's index (weight in kg/(height in m)^2)is $\leq$ 27, having had regular cycles before the menopause, having never received hormone replacement therapy for the menopause or having had a clinically well-tolerated hormone replacement therapy (absence of abnormal bleeding), interrupted for more than 6 weeks, presenting an endometrial thickness measured by endovaginal echography $\leq$ 5 mm, accepting the idea of hormone replacement therapy for the menopause, who would like a hormone therapy without periods, justifying an estroprogestative hormone therapy for at least 6 months, cooperative: accepting to conform to the requirements of the study, whose psychic and intellectual profile would allow one to suppose a good observance of the treatment, having a mammograph dating from less than a year from the date of inclusion.

At the start of treatment the patients undergo an inclusion consultation (C_1) the purpose of which is to verify that the inclusion criteria have been respected, that the endovaginal echograph is normal and to obtain the written consent of the patient as regards participation.

The intermediate consultation (C_2) takes place between the 9th and 11th week of treatment, the purpose of which is to verify mammary and endometrial clinical tolerance is good as regards the treatment.

Lastly, a final consultation (C_3) takes place during the 24th week of treatment.

The patients who wish to continue the study can receive, for 24 additional weeks, the estroprogestative treatment received during the study according to the same therapeutic schema. The extension of the study thus allows a complete monitoring of the study over 48 weeks.

ANALYSIS OF THE STUDY

RESULTS I

The attached Tables I and II, reveal a difference in terms of the amenorrhea results (i.e. no bleeding from 0 to 24 weeks) and of mammary and/or endometrial tolerance as a function of the estrogen.

TABLE I: Treatment A

Nomegestrol acetate + percutaneous 17β-estradiol

Elapse since menopause ameno/month	Presence of HRT previously	Start of treatment	Duration of treatment weeks	Endometrial thickness before/after mm	COMMENTS
72	no	17.10.94	24 24 ext	2/2	amenorrhea endometrial thickness after 48 weeks of treatment = 2 mm
82	no	04.11.94	24 extension	3/3	amenorrhea
26	yes well tolerated	09.01.95	24 extension	3/3	amenorrhea
108	no	16.01.95	24 extension	1/4	amenorrhea
48	no	13.02.95	24	3/2	1 episode of bleeding at 42 days (a few drops) between the 1st and 6th weeks; breast tension and pain of minimal intensity from the 1st to the 22nd week (7days/week) Extension not effected: did not pick up the treatment kit owing to holidays; following the same treatment outside protocol
24	no	10.03.95	24 extension	2/5	amenorrhea; breast tension and pain of slight intensity from the 6th to the 12th week (7 days/week)
55	yes well tolerated	20.03.95	24 extension	4/8	amenorrhea
27	yes well tolerated	08.05.95	24	3/5	amenorrhea Extension not effected: did not pick up the treatment kit owing to holidays; same treatment outside protocol
90	yes well tolerated	10.04.95	24 extension	4/4	amenorrhea
13	yes well tolerated	03.07.95	24 extension	1 pending	amenorrhea
99	yes well tolerated	24.04.95	24 extension	1/4	amenorrhea
21	yes well tolerated	26.06.95	24 extension	4 pending	amenorrhea
96	?	29.05.95	24 extension	2 pending	amenorrhea
65	yes well tolerated	10.05.95	24 extension	1/3	amenorrhea. 10 episodes (4 days/week) of breast pains of minimal intensity
13	no	12.06.95	stopped at 6	3 not measured	continuous slight bleeding from the 5th week until treatment stopped
38	yes well tolerated	10.07.95	24 extension	2 pending	amenorrhea

EXTENSION = 24 additional weeks of treatment

HRT = hormone replacement therapy

CONCLUSION

Of the 16 patients treated:

- 1 left the study, i.e. 6%
- 15 finished the study after 24 weeks, i.e. 94%
- 13 extensions of treatment (24 additional weeks) 81%

The two extensions which did not take place whee due to reasons which were independent of the treatment, the patients continued the same treatment outside the treatment protocol.

TABLE II: Treatment C

Nomegestrol acetate + estradiol valerate per os

Elapse since menopause ameno/month	Presence of HRT previously	Start of treatment	Duration of treatment weeks	Endometrial thickness before/after mm	COMMENTS
12	no	21.11.94	stopped at 8	4/* *=not measured at the control echo	amenorrhea, breast tension and pain of slight intensity from the 2nd week to the 8th week; STOPPED owing to high abdomino-pelvic tension due to increased size of a sub-serous fibroma: echo before treatment = 37 mm; echo after 8 weeks of treatment = 75 mm
46	yes well tolerated	28.11.94	24 extension	3/6	1 episode of bleeding of 31 days between the 5th and the 9th week (a few drops)
31	yes well tolerated	28.11.94	stopped at 10	2 not measured	amenorrhea, STOPPED for insomnia, nervousness and pain in lower limbs
60	yes well tolerated	30.01.95	24 extension	4/2	amenorrhea, breast tension and pain of slight intensity from the 2nd week of treatment until the 19th week
121	yes well tolerated	06.02.95	stopped at 9	3 not measured	1 episode of bleeding of 16 days of low intensity from the 6th week breast tension of minimal intensity from the 2nd week to the 8th week; STOPPED owing to headaches, night sweats and a blood pressure of 17/10
36	yes well tolerated	06.02.95	24	4*	amenorrhea, 23 episodes of breast tension of high intensity of 7 days/week; extension impossible as estrogen dose reduced due to breast tension
47	yes well tolerated	27.02.95	24 extension	2/2	amenorrhea; 6 episodes of breast tension and pain of slight intensity (2 days/week)
62	no	13.03.95	24 extension	1/4	amenorrhea
74	yes well tolerated	20.03.95	24 extension	4/6	amenorrhea
110	yes well tolerated	08.05.95	stopped at 18	2 not measured	amenorrhea until 12 weeks then 1 episode of bleeding of 41 days until treatment stopped
16	yes well tolerated	22.05.95	24 extension	1 pending	amenorrhea
60	yes well tolerated	12.06.95	stopped at 16	2/3	4 episodes of bleeding of low intensity (6 days/week) 5 episodes of breast pain of medium intensity (6 days/week); STOPPED owing to mastitis and a breast abscess
11	no	19.06.95	24 extension	2 pending	1 episode of bleeding 12 days (a few drops)
38	yes well tolerated	03.07.95	stopped at 4	5 not measured	1 episode of bleeding of 11 days until treatment stopped of low intensity

CONCLUSION

Of the 14 patients treated

- 6 left the study i.e. 43%
- 8 finished the study after 24 weeks, i.e. 57%
- 7 extensions of treatment (24 additional weeks), i.e. 50%

% of amenorrhea (i.e. no occurrence of bleeding for 24 weeks) = 43%

RESULTS II

A - OBSERVANCE

While no significant difference exists between the two groups A and C, a lower number of days when treatment lapsed over all the 24 weeks of the study was observed with treatment A.

B - ENDOMETRIAL CLINICAL TOLERANCE

The most significant absolute percentage of amenorrhea is found in group A, the difference being significant in phase II (13th to 24th week of treatment) As has been described in the literature, the percentage of amenorrhea increases with time; therefore, for group C, it is 35.3% during the first 12 weeks of treatment, and 46.1% during the last 12 weeks.

The attached tables III, IV and V illustrate the results obtained.

AMENORRHEA

Analysis regarding treatment

TABLE III: Phase I / weeks 1 to 12

	TOTAL		GROUP A		GROUP C		P
	N	%	N	%	N	%	
Amenorrhea							
yes	19	37.2 %	9	50 %	6	35.3 %	
no	32	62.7 %	9	50 %	11	64.7 %	0.316
Spotting							
yes	32	62.7 %	9	50 %	11	64.7 %	
no	19	37.2 %	9	50 %	6	35.3 %	0.316

None of the patients suffered from metrorrhagias during phase I

	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
Total duration of bleeding (days)	51	9.1±2.1 0:70	18	9.1±4.5 0:70	17	8.9±2.7 0:31	0.412
Average intensity	51	0.8±0.1 0:2	18	0.7±0.2 0:2	17	0.9±0.2 0:2.5	0.446
Number of weeks of bleeding	51	2.1±0.4 0:10	18	1.8±0.7 0:10	17	2.1±0.5 0:7	0.552
Total number of episodes	51	1.2±0.2 0:6	18	1±0.3 0:4	17	1.2±0.4 0:6	0.434

TABLE IV: Phase II / weeks 13 to 24

	TOTAL		GROUP A		GROUP C		P
	N	%	N	%	N	%	
Amenorrhea							
yes	20	42.5 %	12	66.7 %	6	46.1 %	
no	27	57.4 %	6	33.3 %	7	53.8 %	0.006
Spotting							
yes	27	57.4 %	6	33.3 %	7	53.8 %	
no	20	42.5 %	12	66.7 %	6	46.1 %	0.006

None of the patients suffered from metrorrhagias during phase II

	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
Total duration of bleeding (days)	47	13.9±3.1 0:75	18	6.2±3.3 0:42	13	18.5±7.7 0:75	0.013
Average intensity	47	0.9±0.1 0:2	18	0.6±0.2 0:2.33	13	1.0±0.3 0:2	0.055
Number of weeks of bleeding	47	2.9±0.6 0:12	18	1.3±0.6 0:9	13	3.3±1.2 0:11	0.007
Total number of episodes	47	1.3±0.3 0:7	18	0.6±0.3 0:6	13	1.1±0.5 0:7	0.002

TABLE V

Δ % between C1 and C3	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
A.L.A.T.	43	-23.1%±5.2% -88.2%:85.7%	17	-19.0%±3.8% -50%:7.1%	11	-31.2%±13.2% -88.2%:29.4%	0.936
F.S.H.	45	-74.1%±4.9% -98.4%:69.2%	17	-72.2%±5.5% -98%:24.8%	12	-78.2%±9.6% -98.4%:22.8%	0.405
Estradiol (pg/ml)	40	432%±68.5% -54%:1640%	15	567%±118.7% -16%:1320%	10	609%±163.6% -54.3%:1640%	0.036

A.L.A.T. = Alanine Aminotransferase Transaminase

F.S.H. - Follicle Stimulating Hormone

The relative variation in estradiol level is quite important in the two groups (Δ% = 567% in group A and 609% in group c), p = 0.04

Table VI illustrates another study which was carried out. In this other study, it is interesting to note that with nomegestrol acetate, the percentage of patients with absolute amenorrhea (including all forms of estrogenotherapy) is greater from the 3rd month of treatment: 42.5% against 33.3%. In the treatment mentioned above, one must wait until the 12th month of treatment to obtain this percentage of 42% of patients with amenorrhea which was obtained here from 3 months, whilst the populations are comparable in terms of age, weight and length of time since the menopause. In addition, there exists in the previous study, an estrogen effect which is not found in this other study. On the other hand, this study reveals a dosage effect of progestative during the last 9 months of treatment (the lower the dose of progestative the better the cycle is controlled).

Finally, it is interesting to note that no correlation exists between the existence of an amenorrhea at 6 months and the endometrial thickness measured by endovaginal

echography; this thickness varying by +1.6mm on average over 6 months in the 2 treatment groups.

TABLE VI

Characteristics of the patients

	TOTAL		GROUP A		GROUP C		P
	N	avg±week (min:max)	N	avg±week (min:max)	N	avg±week (min:max)	
Age	54	54.9±0.6 45:64	19	53.9±0.8 48:60	17	54.9±1.1 45:63	0.321
Age of amenorrhia (months)	54	56.1±5.0 7:134 60±1.1	19	48.5±7.7 12:108 61.6±1.2	17	50.7±7.7 11:121 60.8±2.2	0.309 0.149
Weight (kg)	54	42:85	19	51:70	17	12:76	
Height	54	1.61±0.01 1.47:1.75	19	1.62±0.01 1.57:1.75	17	1.61±0.02 1.47:1.75	0.449
Quetelet's index (kg/m^2)	54	23.1±0.4 17.1:31.2	19	23.3±0.4 19.7:25.6	17	23.5±0.7 17.5:28.7	0.3182
SBP (mmHg)	54	123.9±1.5 100:140	19	127.9±2.5 110:140	17	121.2±2.5 110:140	0.136
DBP (mmHg)	54	74.6±1.2 60:90	19	76.8±2 60:90	17	73.5±2.3 60:90	0.386

H.R.T.	TOTAL		GROUP A		GROUP C		P
	N	%	N	%	N	%	
Previous HRTs							
yes	17	31.5 %	9	47.4 %	14	82.3 %	
no	37	68.5 %	10	52.6 %	8	17.7 %	0.046

HRT = Hormone Replacement Therapy

SBP = Systolic Blood Pressure

DBP = Diasystolic Blood Pressure

CLAIMS

1. New hormonal pharmaceutical compositions characterized in that they are formed by a combined estroprogestative combination which allows the simultaneous administration of an estrogenic component and a progestative component, in combination or as a mixture with one or more pharmaceutically acceptable, inert, non-toxic excipients, intended for administration by oral route.

2. Estroprogestative compositions according to claim 1, in which the estrogen is free or esterified estradiol or equine conjugated estrogens.

3. Estroprogestative compositions according to claim 1 or claim 2, in which the estrogen is an ester of estradiol and in particular estradiol valerate.

4. Estroprogestative compositions according to one of claims 1 to 3, in which the free or esterified estradiol or an equine conjugated estrogen is present at a dose ranging from 0.5 to 3 mg per unit dose.

5. Estroprogestative compositions according to claim 4, in which the free estradiol is preferably present at a dose of 1.5 mg per unit dose.

6. Estroprogestative compositions according to claim 4, in which the ester of estradiol is preferably present at a dose of 2 mg per unit dose.

7. Estroprogestative compositions according to claim 4, in which the equine conjugated estrogen is preferably present at a dose of 0.625 mg per unit dose.

8. Estroprogestative compositions according to claim 1, in which the progestative is nomegestrol acetate.

9. Estroprogestative compositions according to claims 1 and 8, in which the nomegestrol acetate is present at a dose ranging from 1.5 to 3.75 mg per unit dose.

10. Estroprogestative compositions according to claim 9, in which the nomegestrol acetate is preferably present at a dose of 2.5 mg per unit dose.

11. Use of an estroprogestative mixture according to one of claims 1 to 10, with a view to the production of a medicament intended for the treatment of estrogenic deficiencies in post-menopausal women.

12. Use of an estroprogestative mixture according to one of claims 1 to 10, with a view to the production of a medicament intended for the prevention of osteoporosis and cardiovascular illnesses in post-menopausal women.

13. Use of an estroprogestative mixture according to one of claims 1 to 10, with a view to the production of a medicament intended to be administered to women during their period of ovarian activity in order to stop ovulation.

14. Use of an estroprogestative mixture according to one of claims 1 to 10 with a view to the production of a medicament intended to be administered in a continuous or intermittent fashion.

15. A preparation process for new estroprogestative compositions according to one of claims 1 to 10, which consists of mixing the estrogenic active ingredient and the progestative active ingredient with one or more pharmaceutically acceptable, non-toxic, inert excipients.

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DECLARATION FOR UTILITY OR DESIGN PATENT APPLICATION

☐ Declaration Submitted with Initial Filing OR ☐ Declaration Submitted after Initial Filing

Attorney Docket Number	GEI-067
First Named Inventor	LANQUETIN et al.
COMPLETE IF KNOWN	
Application Number	
Filing Date	
Group Art Unit	
Examiner Name	

As a below named inventor, I hereby declare that:

My residence, post office address, and citizenship are as stated below next to my name

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled :

HORMONAL COMPOSITION CONSISTING OF AN OESTROGEN COMPOUND AND OF A PROGESTATIONAL COMPOUND

(Title of the Invention)

the specification of which

☐ is attached hereto

OR

☐ was filed on (MM/DD/YYYY) October 8, 1997 as United States Application Number or PCT International Application Number PCT/FR97/01792 and was amended on (MM/DD/YYYY) _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment specifically referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations, §1.56

I hereby claim foreign priority benefits under Title 35 United States Code §119 (a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365 (a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number(s)	Country	Foreign Filing Date (MM/DD/YYYY)	Priority Not Claimed	Certified Copy Attached? YES	Certified Copy Attached? NO
96/12239	FRANCE	10/08/96	☐	☐	☐
PCT/FR97/01792	FRANCE	10/08/97	☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐
			☐	☐	☐

☐ Additional foreign application numbers are listed on a supplemental priority sheet attached hereto

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below

Application Number(s)	Filing Date (MM/DD/YYYY)

☐ Additional provisional application numbers are listed on a supplemental priority sheet attached hereto

Burden Hour Statement This form is estimated to take 0 4 hours to complete Time will vary depending upon the needs of the individual case Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, DC 20231 DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS SEND TO: Commissioner of Patents and Trademarks, Washington, DC 20231

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DECLARATION

I hereby claim the benefit under Title 35, United States Code §120 of any United States application(s), or §365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. Parent Application Number	PCT Parent Number	Parent Filing Date (MM/DD/YYYY)	Parent Patent Number *(if applicable)*

☐ Additional U.S. or PCT international application numbers are listed on a supplemental priority sheet attached hereto.

As a named inventor, I hereby appoint the following registered practitioner(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Name	Registration Number	Name	Registration Number
Charles A. Muserlian Jordan B. Bierman Donald C. Lucas	19,683 18,629 31,275		

☐ Additional registered practitioner(s) named on a supplemental sheet attached hereto.

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Name of Sole or First Inventor: ☐ A petition has been filed for this unsigned inventor

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☒ Additional inventors are being named on supplemental sheet(s) attached hereto

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DECLARATION

ADDITIONAL INVENTOR(S) Supplemental Sheet

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Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name	JEAN-LOUIS	Middle Initial		Family Name	THOMAS	Suffix e.g. Jr.	
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Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

Name of Additional Joint Inventor, if any: ☐ A petition has been filed for this unsigned inventor

Given Name		Middle Initial		Family Name		Suffix e.g. Jr.	
Inventor's Signature						Date	
Residence: City		State		Country		Citizenship	
Post Office Address							
Post Office Address							
City		State		Zip		Country	

☐ Additional inventors are being named on supplemental sheet(s) attached hereto

AMENDED CLAIMS according to article 34(2)(b) of the PCT

CLAIMS

1. Hormonal pharmaceutical compositions characterized in that they are formed by a combined estroprogestative combination which allows the simultaneous administration of an estrogenic component and a progestative component, derived from 19-nor progesterone in combination or admixed with one or more pharmaceutically acceptable, inert, non-toxic excipients, intended for administration by oral route.

2. Estroprogestative compositions according to claim 1, in which the estrogen is free or esterified estradiol or equine conjugated estrogens.

3. Estroprogestative compositions according to claim 1 or claim 2, in which the estrogen is an ester of estradiol and in particular estradiol valerate.

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